

THERAPEUTIC POLYANHYDRIDE COMPOUNDS FOR DRUG DELIVERY

Priority of Invention

5 This application is a Continuation of U.S. Patent Application Number
09/917,231, (filed 27 July 2001), which is a Continuation -in-Part of U.S. Patent
Application Number 09/627,215, (filed 27 July 2000), which is incorporated herein
by reference.

Background of the Invention

10 Polymers comprising aromatic or aliphatic anhydrides have been studied
extensively over the years for a variety of uses. For example, in the 1930s fibers
comprising aliphatic polyanhydrides were prepared for use in the textile industry. In
the mid 1950s, aromatic polyanhydrides were prepared with improved film and fiber
15 forming properties. More recently, attempts have been made to synthesize
polyanhydrides with greater thermal and hydrolytic stability and sustained drug
release properties.

 U.S. Patents 4,757,128 and 4,997,904 disclose the preparation of
polyanhydrides with improved sustained drug release properties from pure, isolated
20 prepolymers of diacids and acetic acid. However, these biocompatible and
biodegradable aromatic polyanhydrides have radical or aliphatic bonds resulting in
compounds with slow degradation times as well as relatively insoluble degradation
products unless incorporated into a copolymer containing a more hydrophilic
monomer, such as sebacic acid. The aromatic polyanhydrides disclosed in the '128
25 Patent and the '904 Patent are also insoluble in most organic solvents. A bioerodible
controlled release device produced as a homogenous polymeric matrix from
polyanhydrides with aliphatic bonds having weight average molecular weights
greater than 20,000 and an intrinsic viscosity greater than 0.3 dL/g and a biologically
active substance is also described in U.S. Patent 4,888,176. Another bioerodible
30 matrix material for controlled delivery of bioactive compounds comprising

polyanhydride polymers with a uniform distribution of aliphatic and aromatic residues is disclosed in U.S. Patent 4,857,311.

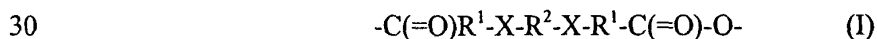
Biocompatible and biodegradable aromatic polyanhydrides prepared from para-substituted bis-aromatic dicarboxylic acids for use in wound closure devices are disclosed in U.S. Patent 5,264,540. However, these compounds exhibit high melt and glass transition temperatures and decreased solubility, thus making them difficult to process. The disclosed polyanhydrides also comprise radical or aliphatic bonds which can not be hydrolyzed by water.

Polyanhydride polymeric matrices have also been described for use in orthopedic and dental applications. For example, U.S. Patent 4,886,870 discloses a bioerodible article useful for prosthesis and implantation which comprises a biocompatible, hydrophobic polyanhydride matrix. U.S. Patent 5,902,599 also discloses biodegradable polymer networks for use in a variety of dental and orthopedic applications which are formed by polymerizing anhydride prepolymers.

Biocompatible and biodegradable polyanhydrides have now been developed with improved degradation, processing and solubility properties, as well as utilities based upon their degradation products.

Summary of the Invention

The present invention provides biocompatible and biodegradable polyanhydrides which serve as the polymeric backbone linking drug molecules into polymeric drug delivery systems. The polyanhydride polymers of the invention demonstrate enhanced solubility and processability, as well as degradation properties due to the use of hydrolyzable bonds such as esters, amides, urethanes, carbamates and carbonates as opposed to radical or aliphatic bonds. The polyanhydride backbone has one or more groups that will provide a therapeutically active compound upon hydrolysis. The polymers of the invention comprise one or more units of formula (I) in the backbone:



wherein each R¹ is group that will provide a therapeutically active compound upon hydrolysis of the polymer; each X is independently an amide linkage, a thioester linkage, or an ester linkage; and R² is a linking group; provided that the therapeutically active compound is not an ortho-hydroxy aryl carboxylic acid.

5 The polyanhydrides of the invention are used to link low molecular weight drug molecules comprising within their molecular structure one carboxylic acid group and at least one amine, thiol, alcohol or phenol group. Accordingly, polyanhydrides of formula (I) serve as the polymer backbone of polymeric drug delivery systems comprising these low molecular weight drugs.

10 Thus, the present invention also relates to compositions, methods of producing compositions and methods of using compositions comprising a polyanhydride of Formula (I) and low molecular weight drug molecules containing within their structure one carboxylic acid group and at least one amine, thiol, alcohol or phenol group, wherein molecules of the drug are linked to one another via
15 the polyanhydride. These polymeric drug delivery systems provide an effective means to deliver drugs in a controlled fashion to any site of a host. By "host" it is meant to include both animals and plants.

The invention also provides a pharmaceutical composition comprising a polymer of the invention and a pharmaceutically acceptable carrier.

20 The invention also provides a therapeutic method for treating a disease in an animal comprising administering to an animal in need of such therapy, an effective amount of a polymer of the invention.

The invention also provides a method of delivering a therapeutically active compound to a host comprising administering to the host a biocompatible and
25 biodegradable polymer of the invention, which degrades into the biologically active compound.

The invention provides a polymer of the invention for use in medical therapy, as well as the use of a polymer of the invention for the manufacture of a medicament useful for the treatment of a disease in a mammal, such as a human.

The invention also provides processes and intermediates disclosed herein that are useful for preparing a polymer of the invention.

Detailed Description of the Invention

5

Definitions

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the
10 straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and
15 one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C₁-C₆)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

20 The term ester linkage means -OC(=O)- or -C(=O)O-; the term thioester linkage means -SC(=O)- or -C(=O)S-; and the term amide linkage means -N(R)C(=O)- or -C(=O)N(R)-, wherein each R is a suitable organic radical, such as, for example, hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl. The term
25 urethane or carbamate linkage means -OC(=O)N(R)- or -N(R)C(=O)O-, wherein each R is a suitable organic radical, such as, for example, hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, aryl, heteroaryl, aryl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl, and the term carbonate linkage means -OC(=O)O-.

The term "amino acid," comprises the residues of the natural amino acids
30 (e.g. Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe,

Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, 5 α -methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g. acetyl or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (e.g. as a (C₁-C₆)alkyl, phenyl or benzyl ester or amide; or as an α - 10 methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & sons, Inc., and references cited therein).

The term "host" includes animals and plants.

15 The term "peptide" describes a sequence of 2 to 35 amino acids (e.g. as defined hereinabove) or peptidyl residues. The sequence may be linear or cyclic. For example, a cyclic peptide can be prepared or may result from the formation of disulfide bridges between two cysteine residues in a sequence. Preferably a peptide comprises 3 to 20, or 5 to 15 amino acids. Peptide derivatives can be prepared as 20 disclosed in U.S. Patent Numbers 4,612,302; 4,853,371; and 4,684,620, or as described in the Examples hereinbelow. Peptide sequences specifically recited herein are written with the amino terminus on the left and the carboxy terminus on the right.

25 Polymers of the Invention

The biocompatible, biodegradable polyanhydrides of the invention are useful in a variety of applications where delivery of a biologically active compound is desired. Examples of such applications include, but are not limited to, medical, dental and cosmetic uses.

The polymers of the invention may be prepared in accordance with methods commonly employed in the field of synthetic polymers to produce a variety of useful products with valuable physical and chemical properties. The polymers can be readily processed into pastes or solvent cast to yield films, coatings, microspheres
5 and fibers with different geometric shapes for design of various medical implants, and may also be processed by compression molding and extrusion.

Medical implant applications include the use of polyanhydrides to form shaped articles such as vascular grafts and stents, bone plates, sutures, implantable sensors, implantable drug delivery devices, stents for tissue regeneration, and other
10 articles that decompose into non-toxic components within a known time period.

Polymers of the present invention can also be incorporated into oral formulations and into products such as skin moisturizers, cleansers, pads, plasters, lotions, creams, gels, ointments, solutions, shampoos, tanning products and lipsticks for topical application.

15 Although the invention provides homopolymers that are prepared from suitably functionalized biologically active compounds, Applicant has discovered that the mechanical and hydrolytic properties of polymers comprising one or more biologically active compounds can be controlled by modifying the linking group (R^2) in the polymer backbone.

20 Preferably, the polymers of the invention comprise backbones wherein biologically active compounds and linker groups (R^2) are bonded together through ester linkages, thioester linkages, amide linkages, or a mixture thereof. Due to the presence of the ester, thioester, and/or amide linkages, the polymers can be hydrolyzed under physiological conditions to provide the biologically active
25 compounds. Thus, the polymers of the invention can be particularly useful as a controlled release source for a biologically active compound, or as a medium for the localized delivery of a biologically active compound to a selected site. For example, the polymers of the invention can be used for the localized delivery of a therapeutic agent to a selected site within the body of a human patient (i.e. within or near a

tumor), where the degradation of the polymer provides localized, controlled, release of the therapeutic agent.

Biodegradable, biocompatible polyanhydrides which serve as linkers for low molecular weight drug molecules have now been developed. Compositions comprising low molecular weight drugs linked via polyanhydrides of the present invention are useful in a variety of applications wherein delivery of the drugs in a controlled fashion is desired. For purposes of the present invention, by "low molecular weight drug" it is meant to include any compound with one carboxylic acid group and at least one amine, thiol, alcohol or phenol group within its structure, wherein the compound has a demonstrated pharmacological activity and a molecular weight of approximately 1000 daltons or less.

In one embodiment, polyanhydrides of the present invention are prepared by the method described in Conix, *Macromol. Synth.*, 2, 95-99 (1996). In this method, dicarboxylic acids are acetylated in an excess of acetic anhydride at reflux temperatures followed by melt condensation of the resulting carboxylic acid anhydride at 180°C for 2-3 hours. The resulting polymers are isolated by precipitation into diethylether from methylene chloride. The described process is essentially the conventional method for polymerizing bisaromatic dicarboxylic acid anhydrides into aromatic polyanhydrides.

Polyanhydrides of the present invention have average molecular weights ranging between about 1500 daltons up to about 100,000 daltons, up to about 100,000 daltons, calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene standards. Preferred aromatic polyanhydrides have average molecular weights of about 1500 daltons, up to about 50,000 daltons calculated by Gel Permeation Chromatography (GPC) relative to narrow molecular weight polystyrene standards. Preferred azo-polymers have average molecular weights of about 1500 daltons, up to about 35,000 daltons.

Biologically Active Compounds

It has been found that the polyanhydride compounds of the invention can serve as a polymer backbone for degradable polymeric drug delivery systems for a multitude of low molecular weight drugs. Drugs which can be linked into degradable copolymers via the polyanhydrides have the following characteristics. The drugs have a relatively low molecular weights of approximately 1,000 daltons or less. The drug must contain within its molecular structure one carboxylic acid group. In addition, the drug must contain at least one carboxylic acid (-COOH), amine (-NHR), thiol (-SH), alcohol (-OH) or phenol (-Ph-OH) group within its structure.

The term "biologically active compound" includes therapeutic agents that provide a therapeutically desirable effect when administered to an animal (*e.g.*, a mammal, such as a human). Therapeutic agents that can be incorporated into the polymers of the invention include suitably functionalized analgesics, anesthetics, anti-Parkinson's agents, anti-infectives, antiacne agents, antibiotics, anticholinergics, anticoagulants, anticonvulsants, antidiabetic agents, antidyskinetics, antifibrotic agents, antifibrotics, antifungal agents, antiglaucoma agents, anti-inflammatory agents, antineoplastics, antiosteoporotics, antipagetics, antispasmodics, antipyretics, antiseptics/disinfectants, antithrombotics, bone resorption inhibitors, calcium regulators, cardioprotective agents, cardiovascular agents, central nervous system stimulants, cholinesterase inhibitors, contraceptives, deodorants, dopamine receptor agonists, erectile dysfunction agents, fertility agents, gastrointestinal agents, gout agents, hormones, hypnotics, immunomodulators, immunosuppressives, keratolytics, migraine agents, motion sickness agents, muscle relaxants, nucleoside analogs, obesity agents, ophthalmic agents, osteoporosis agents, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sclerosing agents, sedatives, skin and mucous membrane agents, smoking cessation agents, sympatholytics, synthetic antibacterial agents, ultraviolet screening agents, urinary tract agents, vaginal agents,

and vasodilators (see Physicians' Desk Reference, 55 ed., 2001, Medical Economics Company, Inc., Montvale, New Jersey, pages 201-202).

In a preferred embodiment, suitable examples of low molecular weight drugs with the required functional groups within their structure can be found in almost all
5 classes of drugs including, but not limited to, analgesics, anesthetics, antiacne agents, antibiotics, synthetic antibacterial agents, anticholinergics, anticoagulants, antidyskinetics, antifibrotics, antifungal agents, antiglaucoma agents, anti-inflammatory agents, antineoplastics, antiosteoporotics, antipagetics, anti-Parkinson's agents, antispasmodics, antipyretics, antiseptics/disinfectants,
10 antithrombotics, bone resorption inhibitors, calcium regulators, keratolytics, sclerosing agents and ultraviolet screening agents.

The biologically active compounds can also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, and carboxylic acids, as well as others) that can be used to modify the properties of the polymer
15 (e.g. for branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the polymer, or for effecting the biodistribution of the polymer). Lists of therapeutic agents can be found, for example, in: Physicians' Desk Reference, 55 ed., 2001, Medical Economics Company, Inc., Montvale, New Jersey; USP Dictionary of
20 USAN and International Drug Names, 2000, The United States Pharmacopeial Convention, Inc., Rockville, Maryland; and The Merck Index, 12 ed., 1996, Merck & Co., Inc., Whitehouse Station, New Jersey. One skilled in the art can readily select therapeutic agents that possess the necessary functional groups for incorporation into the polymers of the invention from these lists.

25 Examples of anti-bacterial compounds suitable for use in the present invention include, but are not limited to, 4-sulfanilamidosalicylic acid, acediasulfone, amfenac, amoxicillin, ampicillin, apalcillin, apicycline, aspoxicillin, aztreonam, bambarmycin(s), biapenem, carbenicillin, carumonam, cefadroxil, cefamandole, cefatrizine, cefbuparazone, cefclidin, cefdinir, cefditoren, cefepime,
30 cefetamet, cefixime, cefmenoxime, cefminox, cefodizime, cefonicid, cefoperazone,

- ceforanide, cefotaxime, cefotetan, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteram, cefibuten, ceftriaxone, cefuzonam, cephalixin, cephaloglycin, cephalosporin C, cephradine, ciprofloxacin, clinafloxacin, cyclacillin, enoxacin, epicillin, flomoxef, grepafloxacin, hetacillin, 5 imipenem, lomefloxacin, lymecycline, meropenem, moxalactam, mupirocin, nadifloxacin, norfloxacin, panipenem, pazufloxacin, penicillin N, pipemidic acid, quinacillin, ritipenem, salazosulfadimidine, sparfloxacin, succisulfone, sulfachrysoidine, sulfaloxic acid, teicoplanin, temafloxacin, temocillin, ticarcillin, tigemonam, tosfloxacin, trovafloxacin, vancomycin, and the like.
- 10 Examples of anti-fungal compounds suitable for use in the present invention include, but are not limited to amphotericin B, azaserine, candicidin(s), lucensomycin, natamycin, nystatin, and the like.
- Examples of anti-neoplastic compounds suitable for use in the present invention include, but are not limited to 6-diazo-5-oxo-L-norleucine, azaserine, 15 carzinophillin A, denopterin, edatrexate, eflornithine, melphalan, methotrexate, mycophenolic acid, podophyllinic acid 2-ethylhydrazide, pteropterin, streptonigrin, Tomudex® (N-((5-(((1,4-Dihydro-2-methyl-4-oxo-6-quinazoliny)methyl)methylamino)-2-thienyl)carbonyl)-L-glutamic acid), ubenimex, and the like.
- 20 Examples of anti-thrombotic compounds for use in the present invention include, but are not limited to, argatroban, iloprost, lamifiban, taprostene, tirofiban and the like.
- Examples of immunosuppressive compounds suitable for use in the present invention include, but are not limited to bucillamine, mycophenolic acid, 25 procodazole, romurtide, ubenimex and the like.
- Examples of NSAID compounds suitable for use in the present invention include, but are not limited to 3-amino-4-hydroxybutyric acid, aceclofenac, alminoprofen, bromfenac, bumadizon, carprofen, diclofenac, diflunisal, enfenamic acid, etodolac, fendosal, flufenamic acid, gentisic acid, meclofenamic acid, 30 mefenamic acid, mesalamine, niflumic acid, olsalazine oxaceprol, S-

adenosylmethionine, salicylic acid, salsalate, sulfasalazine, tolfenamic acid, and the like.

Linking Group "R²"

5 The nature of the linking group "R²" in a polymer of the invention is not critical provided the polymer of the invention possesses acceptable mechanical properties and release kinetics for the selected therapeutic application. The linking group R² is typically a divalent organic radical having a molecular weight of from about 25 daltons to about 400 daltons. More preferably, R² has a molecular weight
10 of from about 40 daltons to about 200 daltons.

The linking group R² typically has a length of from about 5 angstroms to about 100 angstroms using standard bond lengths and angles. More preferably, the linking group L has a length of from about 10 angstroms to about 50 angstroms.

The linking group may be biologically inactive, or may itself possess
15 biological activity. The linking group can also comprise other functional groups (including hydroxy groups, mercapto groups, amine groups, carboxylic acids, as well as others) that can be used to modify the properties of the polymer (e.g. for branching, for cross linking, for appending other molecules (e.g. another biologically active compound) to the polymer, for changing the solubility of the
20 polymer, or for effecting the biodistribution of the polymer).

Specific And Preferred Values

Specific and preferred values listed herein for radicals, substituents, groups, and ranges, are for illustration only; they do not exclude other defined values or
25 other values within defined ranges for the radicals and substituents.

Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₃-C₆)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; (C₃-C₆)cycloalkyl(C₁-C₆)alkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylethyl; (C₁-
30 cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylethyl; (C₁-

C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_1-C_6)alkanoyl can be acetyl, propanoyl or butanoyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or
 5 hexyloxycarbonyl; (C_1-C_6)alkylthio can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, or hexylthio; (C_2-C_6)alkanoyloxy can be acetoxym, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl,
 10 pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific biologically active compound that can be incorporated into the polymers of the invention is 3-amino-4-hydroxybutyric acid, 6-diazo-5-oxo-L-norleucine, aceclofenac, acediasulfone, alminoprofen, amfenac, amoxicillin,
 15 amphotericin B, ampicillin, apalcillin, apicycline, aspoxicillin, azaserine, aztreonam, bambarmycin(s), biapenem, bromfenac, bucillamine, bumadizon, candicidin(s), carbenicillin, carprofen, carumonam, carzinophillin A, cefadroxil, cefamandole, cefatrizine, cefbuperazone, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefminox, cefodizime, cefonicid, cefoperazone,
 20 ceforanide, cefotaxime, cefotetan, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, ceftazidime, cefteteram, ceftibuten, ceftriaxone, cefuzonam, cephalixin, cephaloglycin, cephalosporin C, cephradine, ciprofloxacin, clinafloxacin, cyclacillin, denopterin, diclofenac, edatrexate, eflornithine, enfenamic acid, enoxacin, epicillin, etodolac, flomoxef, flufenamic acid, grepafloxacin,
 25 hetacillin, imipenem, lomefloxacin, lucensomycin, lymecycline, meclofenamic acid, mefenamic acid, melphalan, meropenem, methotrexate, moxalactam, mupirocin, mycophenolic acid, mycophenolic acid, nadifloxacin, natamycin, niflumic acid, norfloxacin, nystatin, oxaceprol, panipenem, pazufloxacin, penicillin N, pipemidic acid, podophyllinic acid 2-ethylhydrazide, procodazole, pteropterin, quinacillin,
 30 ritipenem, romurtide, S-adenosylmethionine, salazosulfadimidine, sparfloxacin,

streptonigrin, succisulfone, sulfachrysoidine, sulfaloxic acid, teicoplanin, temafloxacin, temocillin, ticarcillin, tigemonam, tolfenamic acid, Tomudex® (N-((5-(((1,4-Dihydro-2-methyl-4-oxo-6-quinazolinyl)methyl)methylamino)-2-thienyl)carbonyl)-L-glutamic acid), tosusfloxacin, trovafloxacin, ubenimex or
5 vancomycin.

Another specific value for R² is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.
10

Another specific value for R² is an amino acid.

Another specific value for R² is a peptide

15 Another specific value for R² is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 20 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).

A more specific value for R² is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from the group consisting of (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo, carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.
20
25

Another more specific value for R² is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-) or (-NR-).
30

Another more specific value for R^2 is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 3 to 15 carbon atoms.

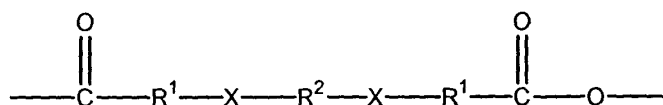
Another more specific value for R^2 is a divalent, branched or unbranched, hydrocarbon chain, having from 3 to 15 carbon atoms.

- 5 A preferred value for R^2 is a divalent, branched or unbranched, hydrocarbon chain, having from 6 to 10 carbon atoms.

A more preferred value for R^2 is a divalent hydrocarbon chain having 7, 8, or 9 carbon atoms.

- A most preferred value for R^2 is a divalent hydrocarbon chain having 8
10 carbon atoms.

A specific polyanhydride linker of the present invention comprises the structure of formula (I):



I

- 15 wherein R^1 is selected from the group consisting of alkyls, cycloalkyls, substituted alkyls, aromatics, substituted aromatics, lactams, and lactones; X is selected from the group consisting of amides, thioamides, esters and thioesters; and R^2 is an alkyl represented by $-(CH_2)_n-$ wherein n is from 1 to 20.

- A specific polyanhydride polymer of the present invention includes
20 biologically active compounds provided that the biologically active compound is not an alpha-hydroxy carboxylic acid.

A specific polyanhydride polymer of the present invention includes biologically active compounds provided that the biologically active compound is not an ortho-hydroxy aryl carboxylic acid.

Such a polymer, wherein each R¹ is a group that will provide a different biologically active compound upon hydrolysis of the polymer, are particularly useful for the administration of a combination of two therapeutic agents to an animal.

5 A preferred group of polyanhydride compounds includes polymers that are comprised of compounds containing at least one free carboxylic acid group, and at least one alcohol group, carboxylic acid or amine group available for reactions which can self-polymerize or co-polymerize with carboxylic acid, alcohol or amine groups or bis(acyl) chlorides.

10

Formulations

 The polymers of the invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally, rectally,
15 or parenterally, by intravenous, intramuscular, intraperitoneal, intraspinal, intracranial, topical, ocular or subcutaneous routes. For some routes of administration, the polymer can conveniently be formulated as micronized particles.

 Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent
20 or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the
25 like. Such compositions and preparations preferably contain at least 0.1% of polymer by weight. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 80% of the weight and preferably 2 to about 60 % of a given unit dosage form. The amount of polymer in such therapeutically useful compositions is such that an effective dosage
30 level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a
5 sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the
10 solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically
15 acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The polymer may also be administered intravenously, intraspinal, intracranial, or intraperitoneally by infusion or injection. Solutions of the polymer
20 can be prepared a suitable solvent such as an alcohol, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

25 The pharmaceutical dosage forms suitable for injection or infusion can include sterile solutions or dispersions or sterile powders comprising the polymer containing the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile,
30 fluid and stable under the conditions of manufacture and storage. The liquid carrier

or vehicle can be a solvent or liquid dispersion medium comprising, for example, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the polymer in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present polymers can be applied in pure form. However, it will generally be desirable to administer them as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include, alcohols or glycols or alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and

other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be
5 employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the polymers of the invention to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith
10 et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Dosages

Useful dosages of the polymers can be determined by comparing their *in vitro* activity, and *in vivo* activity of the therapeutic agent in animal models.
15 Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.
Additionally, useful dosages can be determined by measuring the rate of hydrolysis for a given polymer under various physiological conditions. The amount of a polymer required for use in treatment will vary not only with the particular polymer
20 selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four
25 or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

Combination Therapies

The polymers of the invention are also useful for administering a
30 combination of therapeutic agents to an animal. Such a combination therapy can be

carried out in the following ways: 1) a second therapeutic agent can be dispersed within the polymer matrix of a polymer of the invention, and can be released upon degradation of the polymer; 2) a second therapeutic agent can be appended to a polymer of the invention (i.e. not in the backbone of the polymer) with bonds that hydrolyze to release the second therapeutic agent under physiological conditions; 3) the polymer of the invention can incorporate two therapeutic agents into the polymer backbone (e.g. a polymer comprising one or more units of formula (I)) or 4) two polymers of the invention, each with a different therapeutic agent can be administered together (or within a short period of time).

Thus, the invention also provides a pharmaceutical composition comprising a polymer of the invention and a second therapeutic agent that is dispersed within the polymer matrix of a polymer of the invention. The invention also provides a pharmaceutical composition comprising a polymer of the invention having a second therapeutic agent appended to the polymer (e.g. with bonds that will hydrolyze to release the second therapeutic agent under physiological conditions).

The polymers of the invention can also be administered in combination with other therapeutic agents that are effective to treat a given condition to provide a combination therapy. Thus, the invention also provides a method for treating a disease in a mammal comprising administering an effective amount of a combination of a polymer of the invention and another therapeutic agent. The invention also provides a pharmaceutical composition comprising a polymer of the invention, another therapeutic agent, and a pharmaceutically acceptable carrier.

Preparation Of Polymers Of The Invention

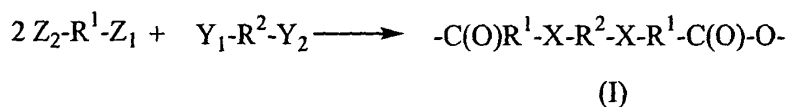
Processes for preparing polyanhydride polymers of the invention are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.

For example, a polymer of the invention can be prepared, as illustrated in Scheme I, from a biologically active compound of formula ($Z_1-R^1-Z_2$) and a linker

precursor of formula $Y_1-R^2-Y_2$, wherein one of Z_1 , and Z_2 is a carboxylic acid group and the other groups Y_1 , Y_2 , Z_1 , and Z_2 are independently selected from the values in the table below.

5

Scheme I



The biologically active compound and the linker precursor can be polymerized using well known synthetic techniques (e.g. by condensation) to provide a polymer of the invention (I) wherein each X is independently an ester linkage, a thioester linkage, or an amide linkage.

10

Depending on the reactive functional group (Z_1 , and Z_2) of the biologically active compound, a corresponding functional group (Y_1 or Y_2) can be selected from the following table, to provide an ester linkage, thioester linkage, or amide linkage in the polymer backbone.

15

	Functional Group On Biologically active compound (Z_1 or Z_2)	Functional Group On Linker Precursor (Y_1 or Y_2)	Resulting Linkage In Polymer
20	-COOH	-OH	Ester
	-COOH	-NHR	Amide
	-COOH	-SH	Thioester
	-OH	-COOH	Ester
	-SH	-COOH	Thioester
25	-NHR	-COOH	Amide

As will be clear to one skilled in the art, suitable protecting groups can be used during the reaction illustrated in Scheme I (and in the reactions illustrated in

Schemes II-XV below). For example, other functional groups present in the biologically active compound or the linker precursor can be protected during polymerization, and the protecting groups can subsequently be removed to provide the polymer of the invention. Suitable protecting groups and methods for their incorporation and removal are well known in the art (see for example Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & sons, Inc.).

Additionally, when a carboxylic acid is reacted with a hydroxy group, a mercapto group, or an amine group to provide an ester linkage, thioester linkage, or an amide linkage, the carboxylic acid can be activated prior to the reaction, for example, by formation of the corresponding acid chloride. Numerous methods for activating carboxylic acids, and for preparing ester linkages, thioester linkages, and amide linkages, are known in the art (see for example Advanced Organic Chemistry: Reaction Mechanisms and Structure, 4 ed., Jerry March, John Wiley & Sons, pages 419-437 and 1281).

A polyanhydride/polyester of the invention can be formed from a hydroxy/carboxylic acid containing compound of formula (HOOC-R¹-OH) and from a linker precursor of formula HOOC-R²-COOH as illustrated in Scheme 2.

20

SCHEME 2



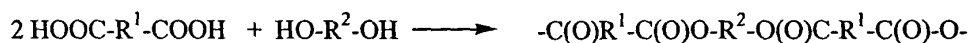
A polyanhydride/polyamide of the invention can be prepared using a procedure similar to that illustrated in Scheme 2 by replacing the biologically active hydroxy/carboxylic acid compound in Scheme 2 with a suitable biologically active amine/ carboxylic acid compound.

A polyanhydride/polythioester of the invention can be prepared using a procedure similar to that illustrated in Scheme 2 by replacing the biologically active

hydroxy/carboxylic acid compound in Scheme 2 with a suitable mercapto/carboxylic acid compound.

Alternatively, a polyanhydride/polyester of the invention can be formed from a dicarboxylic acid containing compound of formula $\text{HOOC-R}^1\text{-COOH}$ and from a diol linker precursor of formula $(\text{HO-R}^2\text{-OH})$ as illustrated in Scheme 3.

SCHEME 3



(III)

10 A polyanhydride/polyamide of the invention can be prepared using a procedure similar to that illustrated in Scheme 2 by replacing the diol linker compound in Scheme 3 with a suitable diamine compound.

A polyanhydride/polythioester of the invention can be prepared using a procedure similar to that illustrated in Scheme 2 by replacing the diol linker
15 compound in Scheme 3 with a suitable dimercapto compound.

Other polymers of the invention can be formed using the reactions described herein, using starting materials that have suitable groups to prepare the desired polymer.

Polymeric drug delivery systems of the present invention can be
20 characterized by proton nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, gel permeation chromatography (GPC), high performance liquid chromatography (HPLC), differential scanning calorimetry (DSC), and thermal gravimetric analysis (TGA). For infrared spectroscopy, samples are prepared by solvent casting on NaCl plates. ^1H and ^{13}C NMR spectroscopy is obtained in
25 solutions of CDCl_3 or DMSO-d_6 with solvent as the internal reference.

GPC is performed to determine molecular weight and polydispersity. In this method, samples are dissolved in tetrahydrofuran and eluted through a mixed bed

column (PE PL gel, 5 μ m mixed bed) at a flow rate of 0.5 mL/minute. It is preferred that the samples (about 5 mg/mL) be dissolved into the tetrahydrofuran and filtered using 0.5 μ m PTFE syringe filters prior to column injection. Molecular weights are determined relative to narrow molecular weight polystyrene standards (Polysciences, Inc.).

Thermal analysis can also be performed using a system such as the Perkin-Elmer system consisting of a TGA 7 thermal gravimetric analyzer equipped with PE AD-4 autobalance and Pyris 1 DSC analyzer. In this system, Pyris software is used to carry out data analysis on a DEC Venturis 5100 computer. For DSC, an average sample weight of 5-10 mg is heated at 10°C/minute at a 30 psi flow of N₂. For TGA, an average sample weight of 10 mg is heated at 20°C/minute under a 8 psi flow of N₂. Sessile drop contact angle measurements are obtained with an NRL Goniometer (Rame-hart) using distilled water. Solutions of polymer in methylene chloride (10% wt/volume) are spun-coated onto glass slips, at 5,000 rpm for 30 seconds.

Degradation and drug release profiles of the polymer drug delivery systems of the present invention can also be determined routinely. For these experiments, the polymers are processed into either films, pellets, microspheres, nanospheres or fibers (depending on their properties). After processing, the materials are characterized to determine if any physicochemical changes have occurred during processing. Uniform processed, weighed, and characterized samples are then degraded in acidic, neutral, and basic phosphate buffer (conditions chosen to simulate physiological range) in triplicate. Periodically the buffer is removed and replaced with fresh media to simulate sink conditions. The spent buffer is analyzed by HPLC to determine the cumulative release of the drug. At defined time periods, samples are removed from the buffer and superficially dried (blotted). They are then weighed to determine the water uptake. At this point, the contact angle (hydrated) is also measured to determine changes in hydrophobicity during degradation. The samples are then thoroughly dried under vacuum and weighed to determine their mass loss. Contact angles (dry) are measured again to determine the hydrophobicity

of the dry material, and how it compares to that of the hydrated material. By plotting cumulative release of the degradation products over time, the degradation kinetics can be defined. Wet and dry polymer weights over time indicate if the material is bulk or surface eroding. If there is an increase in water uptake, it can be
5 determined that the polymer is bulk eroding, whereas if there is little or no water uptake the material is considered surface-eroding. By plotting the changes in dry weight versus time, the mass lost by the polymer as it erodes can be determined. This information will give additional insight into how the material is degrading. Changes in molecular weight over time are also examined to bolster the degradation
10 results.

Polyanhydride compounds of the present invention can be isolated by known methods commonly employed in the field of synthetic polymers and used to produce a variety of drug delivery products with valuable physical and chemical properties. Polymeric drug delivery systems comprising the polyanhydride compounds of the
15 invention can be readily processed into pastes or solvent cast to yield films, coatings, microspheres and fibers with different geometric shapes for design of various medical implants, and may also be processed by compression molding and extrusion. Medical implant applications include the use of polyanhydrides to form shaped articles such as vascular grafts and stents, bone plates, sutures, implantable
20 sensors, implantable drug delivery devices, stents for tissue regeneration, and other articles that decompose harmlessly while delivering a selected low molecular weight drug at the site of implantation within a known time period. Drugs linked via these polyanhydrides of the present invention can also be incorporated into oral formulations and into products such as skin moisturizers, cleansers, pads, plasters,
25 lotions, creams, gels, ointments, solutions, shampoos, tanning products and lipsticks for topical application.

The quantity of polymeric drug to be administered to a host which is effective for the selected use can be readily determined by those of ordinary skill in

the art without undue experimentation. The quantity essentially corresponds stoichiometrically to the amount of drug which is known to produce an effective treatment for the selected use.

The present invention also relates to methods of using compositions comprising these low molecular weight drugs linked via the polyanhydrides in any application wherein delivery of the low molecular weight drug is desired. Route of delivery is selected in accordance with drug being administered and the condition being treated. For example, compositions of the present invention comprising a polyanhydride of Formula (I) linking a low molecular weight drug such as, for example, amoxicillin or cephalexin can be administered orally or topically to treat bacterial infections. Similarly, compositions of the present invention comprising a polyanhydride of Formula (I) linking a low molecular weight drug such as carbidopa or levodopa can be administered orally to patients suffering from Parkinson's disease to alleviate the symptoms of this disease.

In one embodiment of the present invention, the polyanhydride of Formula (I) is used to link two different low molecular weight drugs into a single polymeric drug delivery system. For example, the polyanhydride of Formula (I) can be used to link a drug molecule of carbidopa with a drug molecule of levodopa so that both drugs can be delivered simultaneously via a single polymeric drug delivery system.

Another embodiment of the present invention includes a method of linking low molecular weight drug molecules containing within their structure one carboxylic acid group and at least one amine, thiol, alcohol or phenol group into polymeric drug delivery systems comprising; (a) protecting the carboxylic acid group of the lowmolecular weight drug molecules; (b) adding to the low molecular weight drug molecules a chlorinated polyanhydride linker of formula (IV)



wherein n is from 1 to 20, so that drug molecules displace the chlorine groups of the polyanhydride linker of Formula (IV) and bind to the linker via their amine, thiol, alcohol or phenol group; and (c) exposing the linked drug molecules to heat or vacuum so that the protecting groups are removed. In a preferred compound of formula (IV) n is from 6-8.

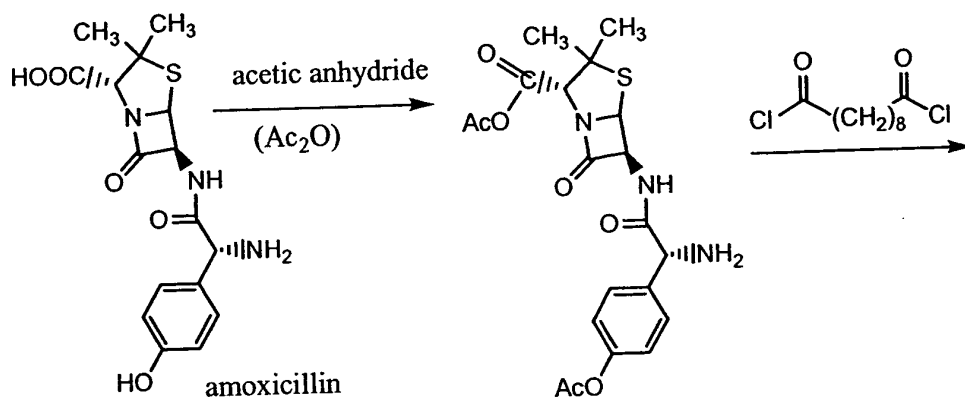
The linking of a drug in an anhydride polymer of the present invention is shown in the following schemes. The carboxylic acid group of the low molecular weight drug molecule is protected, preferably via acetylation. The protected drug molecules are then exposed to the linker of the linker of formula (IV), optionally in an activated form, e.g., the chlorinated form and bind to the linker (R^2) via the amine, thiol, alcohol or phenol groups of the drug molecules. The drug and linker are then exposed to heat and/or vacuum to remove the protecting groups, thereby resulting in a polymeric drug delivery system. The polymers of the invention will have from about 10 to about 30 repeating units.

The linkage of low molecular weight drugs meeting the structural requirements of a single carboxylic acid group and at least one amine, thiol, alcohol or phenol group within its structure are exemplified in the following Examples 1 and 2.

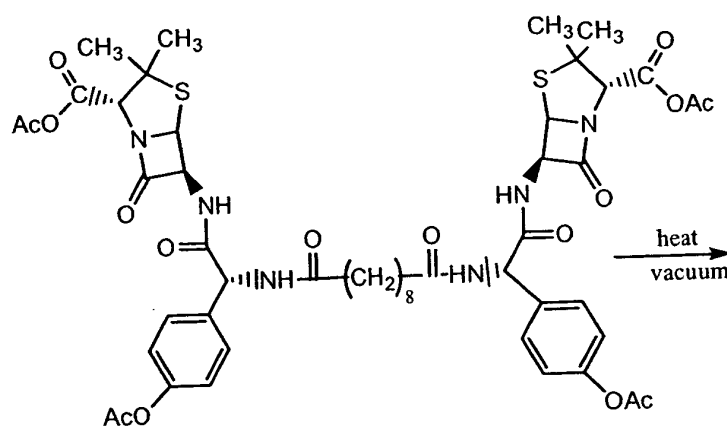
Example 1 Synthesis of Amoxicillin Polymer

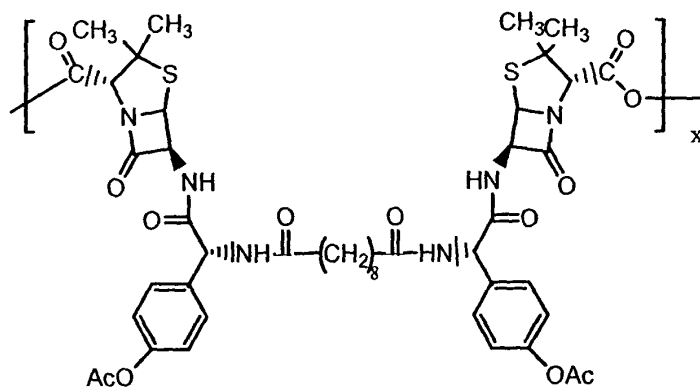
The linkage of amoxicillin in a polyanhydride of the present invention is shown in the scheme 1. The carboxylic acid group of the low molecular weight drug molecule is protected, preferably via acetylation. The protected drug molecules are then exposed to a chlorinated form of the linker of formula (IV), wherein n is 8. The amine groups from the drug molecules displace the chlorine groups of the diacyl halide Formula (IV) and bind to the linker(R^2) via the amine, groups of the drug molecules. The linked drug is exposed to heat and/or vacuum to remove the protecting groups, thereby resulting in a polymeric drug delivery system.

Scheme 1



5



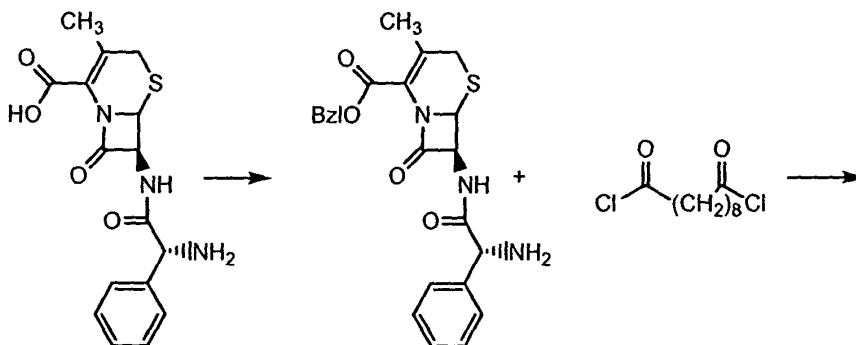


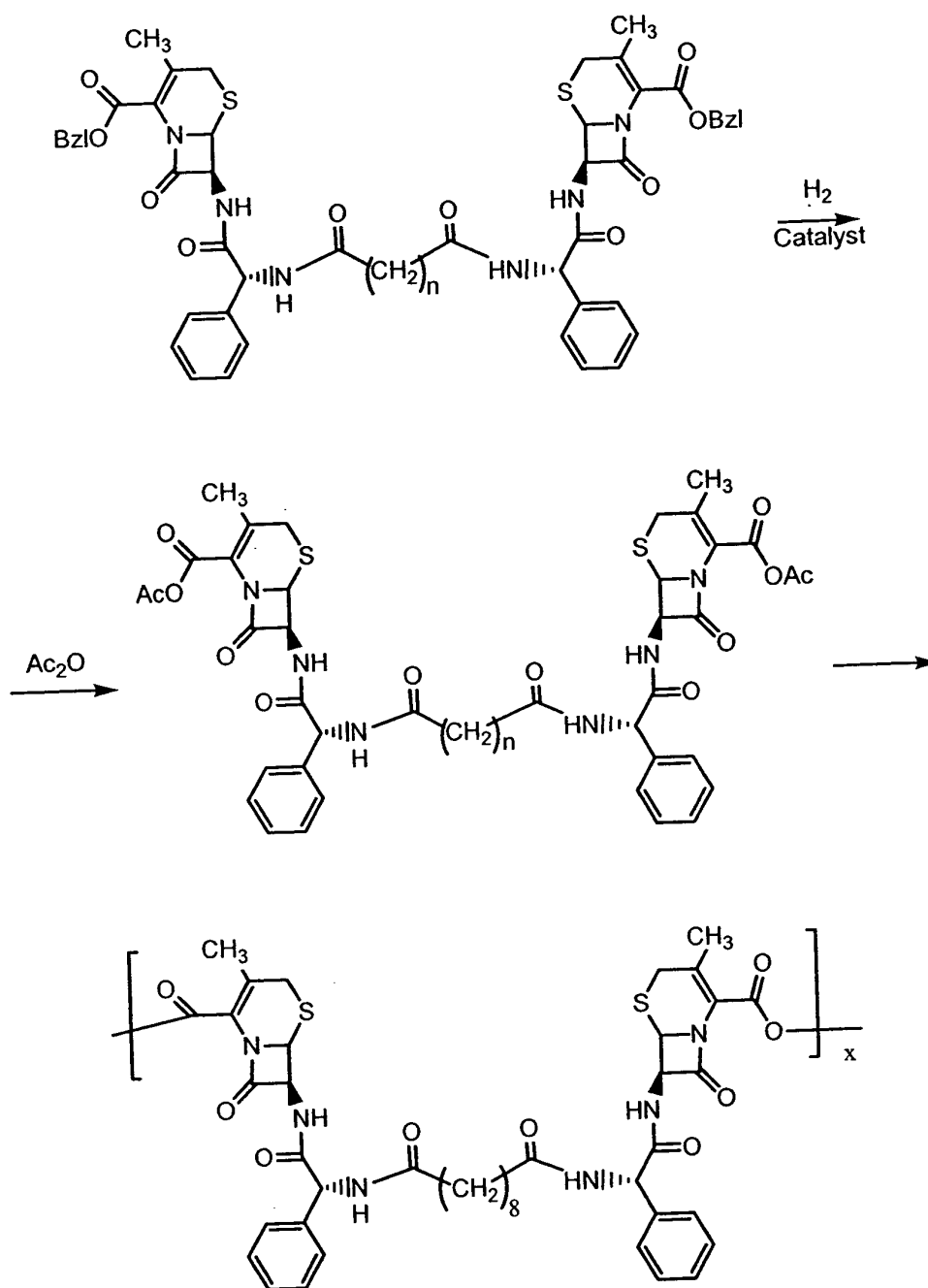
Example 2 Synthesis of Cephalexin Polymer

A cephalexin polymer is prepared as depicted in scheme 2. The carboxylic acid group of cephalexin is first protected, for example with a benzylic group. The drug is then linked to sebacoyl chloride (formula (IV) where n is 8). Following this linkage, the protecting groups are removed to produce carboxylic acids which are then acetylated to produce monomer. The monomer is polymerized as a melt.

10

Scheme 2



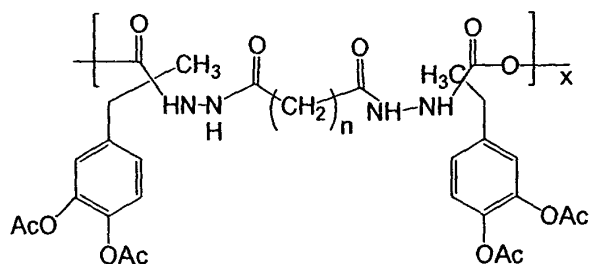


Example 3

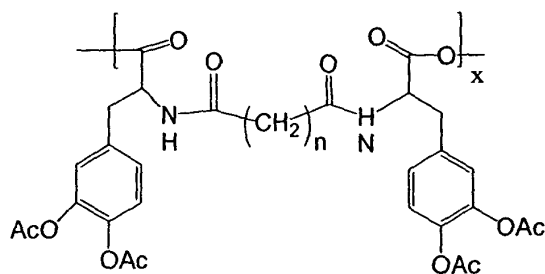
- 5 Other polymeric drug delivery systems can be prepared in accordance with this method via the polyanhydride linker of Formula (I) of the present invention

include, but are certainly not limited to, a carbidopa delivery system, a levodopa delivery system and an amtenac delivery system. Homopolymers of the carbidopa and levodopa drug delivery systems are depicted in Formulas (V) and (VI), respectively

5



(V)



(VI)

10

While these structures depict homopolymers, copolymers of such drugs can also be prepared routinely based upon the teachings provided herein. Further, polymeric drug delivery systems comprising the polyanhydride of Formula (I) and other drugs meeting the structural requirements, namely one carboxylic acid group, at least one amine, thiol, alcohol or phenol group, and having a molecular weight of approximately 1000 daltons or less can also be routinely prepared via the disclosed methods.

Activity

The ability of a polymer of the invention to produce a given therapeutic effect can be determined using *in vitro* and *in vivo* pharmacological models which are well known to the art.

5

All publications, patents, and patent documents (including the entire contents of U.S. Provisional Patent Application Number 60/220,998 , filed 27 July 2000) are incorporated by reference herein, as though individually incorporated by reference.

The invention has been described with reference to various specific and preferred
10 embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

15